

Dean L. Engelhardt et al., Serial No.: 08/486,069 (Filed: June 7, 1995)

Page 145 [Fourth Supplemental Amendment To Applicants' December 31, 2003 Amendment – January 21, 2005]

**REMARKS**

This paper follows a brief telephonic interview held on January 20, 2005 between Examiner Ardin H. Marschel, Ph.D.<sup>2</sup> and Applicants' undersigned attorney. During the telephone call, the possibility of canceling several claims and amending other claims was discussed for the purpose of narrowing, if not resolving, the outstanding issues in this application. Thus, this paper implements the substance of that interview.

**I. Claim Changes****A. *Claim Cancellations***

As discussed during the telephonic interview, Applicants have canceled, by this paper, claims 1298-1328, 1331-1332, 1334-1351, 1353-1354, 1357-1358, 1360, 1362-1369, 1372-1380, 1383, 1386-1391, 1393-1407, 1409-1410, 1583-1585, 1587, 1592-1612, 1614-1615, 1618-1621, 1623-1628, 1631-1632, 1635-1647, 1649-1656, 1658, 1660-1667, 1670-1677, 1679-1680, 1682, 1685-1699 and 1725-1726. The cancellation of these claims has been done without prejudice or disclaimer to Applicants' right to pursue the subject matter of these claims at some future yet undefined point in time. Claims 1298 *et seq.* were directed to a process for detecting a nucleic acid of interest; and claims 1582 *et seq.* were directed to a process for preparing a detectable non-radioactively labeled oligo- or polynucleotide of interest. In each of claims 1298 and 1582, *Sig*, the detectable non-radioactive label moiety was recited to be "non-nucleotidyl." With the aforementioned cancellations, the blocks of claims running from 1298-1410 and 1582-1699 have been canceled. Two other claims that formerly depended from now canceled claims have also been canceled. These include claims 1758 and 1759. Both recited dependencies from "claims 1373 or 1671."

---

<sup>2</sup> Dr. Marschel was recently appointed Supervisory Patent Examiner (SPE) for Group Art Unit 1631.

Dean L. Engelhardt et al., Serial No.: 08/486,069 (Filed: June 7, 1995)

Page 146 [Fourth Supplemental Amendment To Applicants' December 31, 2003 Amendment – January 21, 2005]

**B. *Claim Amendments***

To conform with the just-described claim cancellations, two other claims have been amended. These include claims 1757 and 1760. In the former claim, references to now canceled claims 1354, 1356, 1652 and 1654 have been expunged. In the latter, references to now canceled claims 1298 and 1582 have also been removed.

**C. *Other Claim Amendments***

While implementing the changes to the claim above, Applicants' attorney noticed other minor errors or inconsistencies in the claims that have also been corrected. These other amended claims include:

- Claim 918 (insertion of "or" between the two chemical structures);
- Claims 950-951 (Canceled) [Previously "Claims 950-952" were listed as having been canceled.];
- Claim 1179 (deletion of claim "1182" leaving this claim dependent from claim 1178);
- Claim 1190 (deletion of "1189" leaving this claim dependent from claim 1185);
- Claim 1193 (dependency changed from claim "1191" to -- 1192 --);
- Claim 1707 (deletion of "and" between the detecting and comparing steps); and
- Claim 1710 (insertion of "and" between the comparing and detecting steps).

It is believed that none of the foregoing amendments to the claims raises any issue of new matter. Entry of these claim amendments and claim cancellations is respectfully requested.

Enz-5(D8)(C2)

Dean L. Engelhardt et al., Serial No.: 08/486,069 (Filed: June 7, 1995)

Page 147 [Fourth Supplemental Amendment To Applicants' December 31, 2003 Amendment – January 21, 2005]

II. Status of Claims After Entry

After entry of the claims identified in the complete listing above, the status of the claims will be as follows:

Claims presently amended above: 918, 1179, 1190, 1193, 1707, 1710, 1757 and 1760.

Claims canceled above: 1298-1328, 1331-1332, 1334-1351, 1353-1354, 1357-1358, 1360, 1362-1369, 1372-1380, 1383, 1386-1391, 1393-1407, 1409-1410, 1583-1585, 1587, 1592-1612, 1614-1615, 1618-1621, 1623-1628, 1631-1632, 1635-1647, 1649-1656, 1658, 1660-1667, 1670-1677, 1679-1680, 1682, 1685-1699, 1725-1726 and 1758-1759.

New claims added above: None

Pending claims presented for further examination: 569-571, 573-575, 577, 582-589, 592-594, 597-600, 602-604, 607-608, 610-612, 614-624, 634-635, 637-638, 641-642, 646, 648-651, 656-661, 667, 670, 707-714, 716-717, 719-723, 725-727, 729, 734-747, 749-752, 754-756, 759-760, 762-764, 766-776, 786-787, 789-790, 793-794, 796-797, 800-803, 808-813, 819, 822, 859-866, 868-869, 871-875, 877-879, 881, 886-899, 901-904, 906-908, 911-912, 914-916, 918-928, 938-939, 941-942, 945-949, 952-955, 960-965, 971, 974, 1011-1018, 1020-1021, 1023-1027, 1029-1031, 1033, 1038-1051, 1053-1056, 1058-1060, 1063-1064, 1066-1068, 1070-1080, 1090-1091, 1093-1094, 1097-1099, 1101, 1104-1107, 1112-1117, 1123, 1126, 1163-1170, 1172-1173, 1175-1179, 1181-1183, 1185, 1190-1200, 1204, 1208-1209, 1212-1216, 1218-1244, 1248-1249, 1253, 1255-1258, 1263-1270, 1272, 1275, 1278-1294, 1296-1297, 1411-1487, 1490-1491, 1493-1516, 1518, 1520-1525, 1527, 1530-1539, 1541, 1544-1568, 1570-1581, 1700-1724, 1727-1757 and 1760-1796.

Before closing, Applicants' attorney thought it might be helpful to list the rejections and issues raised in the July 1, 2003 Office Action, and Applicants' actions or arguments in response.

Enz-5(D8)(C2)

Dean L. Engelhardt et al., Serial No.: 08/486,069 (Filed: June 7, 1995)

Page 148 [Fourth Supplemental Amendment To Applicants' December 31, 2003 Amendment – January 21, 2005]

### **III. Brief Summary of the Rejections and Issues in the July 1, 2003 Office Action**

#### **A. Denial of Request for Interference filed 12/21/01 (Office Action, pages 2-4)**

In their September 28, 2004 Request for Interference Pursuant To 37 C.F.R. §41.202, Applicants' attorneys submitted two counts in McKelvey format, taking into consideration the discussions held at the September 21, 2004 interview. In Count 1, Applicants submitted their sequencing claim wherein one or more fluorescent indicators are covalently attached to one or more nucleotides in detectable non-radioactively labeled nucleic acid fragments. In Count 2, Applicants' sequencing claim calls for using detectable non-radioactively labeled nucleic acid fragments that have been labeled by the incorporation of one or more nucleoside triphosphates comprising different fluorescent indicators. It is believed that the submission of Applicants' September 28, 2004 Request for Interference obviates the grounds for denying entry of Applicants' first Request for Interference request filed on December 21, 2001.

#### **B. Requirement for a shorter replacement abstract (page 4)**

A replacement abstract containing fewer than 150 words was submitted with Applicants' December 31, 2003 Amendment. This replacement abstract obviated the objection set forth in the July 1, 2003 Office Action.

#### **C. New Matter**

##### **1) chemical linkage to base, sugar or phosphoric acid component (pages 4-5)**

In their December 31, 2003 Amendment (page 10, first two paragraphs), Applicants traversed the rejection for new matter, but they amended several claims in response to the Examiner's rejection. As in the case of the claims presented in their December 31, 2003 Amendment, Applicants' presently pending claims recite that the Sig label moiety is attached via an amine linkage, a glycosidic linkage or an olefinic bond only for nucleotide structure (i) in which the base moiety is labeled.

Enz-5(D8)(C2)

Dean L. Engelhardt et al., Serial No.: 08/486,069 (Filed: June 7, 1995)

Page 149 [Fourth Supplemental Amendment To Applicants' December 31, 2003 Amendment – January 21, 2005]

2) different indicator molecules (page 5)

As explained by Applicants' attorney at the September 21, 2004 interview, different fluorescent labels and different colored labels are disclosed in Example 9 in the '069 specification:<sup>3</sup>

I. Karyotyping

(a) Select from a human gene library some 100 to 200 clones. Label them as described above, and for each clone locate its place or places of hybridization visually or with a low-light-level video system. For those clones which correspond to a unique sequence gene this determines the location of the cloned DNA on a particular human chromosome. Obtain several clones for each chromosome. Each of these labeled clones can be used to identify particular chromosomes. They can also be used in combination to identify each of the 46 chromosomes as being one of the 22 autosomal pairs or the X or the Y. By allowing one set of labeled clones to hybridize to the chromosomes and then adding a fluorescent stain to the label, the set of clones and their locations can be visualized and will fluoresce with a particular color. A second set of labeled clones could then be used and reacted with a second fluorescent dye. The same process can be repeated a number of times. Thus one can, if desired, have several sets of fluorescent labels attached to the cellular DNA at different but specific locations on each of the chromosomes. These labels could be used for visual or computerized automatic karyotyping. [emphasis added]

Furthermore, indicator molecules are explicitly described in the specification on page 25:

... If avidin is coupled to potentially demonstrable indicator molecules, e.g., fluorescent dyes (fluorescein, rhodamine), electron dense reagents (ferritin, hemocyanin, colloidal gold), or enzymes capable of depositing insoluble reaction products (peroxidase, alkaline phosphatase) the presence, location and/or quantity of the biotin probe can be established. [emphasis added]

It is believed, therefore, that the subject matter directed to "different indicator molecules" is supported by Applicants' specification.

D. Enablement (furanosyl) (pages 6-8)

As indicated in their December 31, 2003 Amendment (page 11, first paragraph), while disagreeing that the term "sugar" is not fully enabled, nevertheless Applicants amended the claims to satisfy the Examiner. Thus, the term "sugar" has been substituted with the term "furanosyl

<sup>3</sup> This point was also raised in Applicants' December 31, 2003 Amendment (see page 6); and in the Supplemental Declaration of Dr. James J. Donegan (see Paragraph 11, Section A (i), beginning on page 7, and continuing through page 8, first two paragraphs).

Dean L. Engelhardt et al., Serial No.: 08/486,069 (Filed: June 7, 1995)

Page 150 [Fourth Supplemental Amendment To Applicants' December 31, 2003 Amendment – January 21, 2005]

moiety" in all the presently pending claims. Accordingly, it is believed that the enablement rejection has been obviated by previous amendments to the claims.

**E. Vagueness and Indefiniteness (pages 8-11)**

**1) antecedent basis for "indicator molecules" (pages 8-9)**

As explained in their July 13, 2004 Supplemental Amendment, Applicants amended several claims to clarify the relationship between the detectable non-radioactive moieties A or Sig and the indicator molecules. The amended claims included 657, 809, 961, 1113, 1264, 1373, 1445, 1531, 1544 and 1671. Of the foregoing claims, 1373 and 1671 have been canceled above by this paper. All of the remaining claims except claim 1445 recite that "said A or said Sig is a non-radioactively detectable indicator molecule." In the case of the one exception, claim 1445 recites that "said non-radioactively detectable protein comprises a signalling component or indicator molecule." Given the nature of the non-radioactively detectable protein recited in the process of claim 1445, the open-ended language with respect to the signalling component or indicator molecule is believed to be appropriate.

**2) nucleotide analogs, sugar analog, phosphate analog and base analog (pages 9-11)**

As described in Applicants' July 13, 2004 Supplemental Amendment, the matter of nucleotide analogs was discussed at the April 1, 2004 interview. Applicants' attorney explained that the term "nucleotide analog" is a term long recognized in the art, citing the textbooks of Dr. Arthur Kornberg [DNA Synthesis (1974) and DNA Replication (1980)] and Prof. Dr. Karl Heinz Scheit [Nucleotide Analogs: Synthesis and Biological Function (1980)]. He also explained that Kornberg's "nucleotide analogs" were defined as those molecules that could be incorporated into DNA or RNA. Furthermore, "base analogs" and various related terms are recited in some dependent claims. The terms "sugar analog" and "phosphate analog" no longer appear in the presently pending claims.

**3) non-radioactively labeled fragments (page 11)**

As a follow-up to the April 1, 2004 interview and in response to the July 1, 2003 Office Action, various pending claims recite "modified or labeled nucleotides or *modified or labeled*

Enz-5(D8)(C2)

Dean L. Engelhardt et al., Serial No.: 08/486,069 (Filed: June 7, 1995)

Page 151 [Fourth Supplemental Amendment To Applicants' December 31, 2003 Amendment – January 21, 2005]

*nucleotide analogs.*" In view of the foregoing language, a clear antecedent basis has been formed for "non-radioactively labeled fragments" in the claims.

**F. Anticipation of Claim 1411 by Kourilsky et al. (pages 12-13)**

The rejection of claim 1411 for anticipation by the two Kourilsky patent documents is believed to have been handled by the claim changes submitted in Applicants' December 31, 2003 Amendment. As worded then and as stated in present claim 1411, the non-radioactively detectable protein (ii) is non-radioactive and has a binding affinity to said operator sequence in the oligo- or polynucleotide (i).

**G. Anticipation Rejection of Claim 1582 by Dunn et al. (1977) (pages 13-14)**

The cancellation of claims 1582 *et al.* above is believed to have rendered the Dunn anticipation rejection moot.

**H. Obviousness Rejection of Claim 1411 over Langer et al. (1981) or Dale et al. (1975)**

As in the case of the first anticipation rejection based on the Kourilsky patent disclosures, the obviousness rejection of claim 1411 *et al.* is believed to have been obviated by the changes presented in Applicants' December 31, 2003 Amendment. The wording of present claim 1411 now includes a non-radioactively detectable protein (ii) that is non-radioactive and has a *binding affinity to the operator sequence* in the oligo- or polynucleotide (i).

**I. Obviousness Rejection of Claims 1298 and 1411**

Claims 1298 *et al.* have been canceled and claims 1411 *et al.* have been previously amended to recite a non-radioactively detectable protein (ii) that is non-radioactive and has a *binding affinity to the operator sequence* in the oligo- or polynucleotide (i).

Early and favorable action is respectfully requested.

\* \* \* \* \*

Enz-5(D8)(C2)

Dean L. Engelhardt et al., Serial No.: 08/486,069 (Filed: June 7, 1995)

Page 152 [Fourth Supplemental Amendment To Applicants' December 31, 2003 Amendment – January 21, 2005]

CONCLUSION

In light of the above claim cancellations, Applicants believe that no additional fees are due in connection with this paper. No new claims have been added and the total number of claims pending in this application is less than the number of previously paid for claims. In the event that any additional fees are due, however, Applicants hereby requests that the Patent and Trademark Office charge the amount of any such fees to Deposit Account No. 05-1135.

Early and favorable action is respectfully requested.

If a telephone conversation would further prosecution of the application, the Examiner is welcome to call Applicant's undersigned attorney at the number below.

January 21, 2005

Respectfully submitted,



Ronald C. Fedus

Registration No. 32,567

Natalie Bogdanos

Registration No. 51,480

ENZO LIFE SCIENCES, INC.  
c/o ENZO BIOCHEM, INC.  
527 Madison Avenue, 9<sup>th</sup> Floor  
New York, NY 10022-4304  
Telephone: (212) 583-0100  
Facsimile: (212) 583-0150

Enz-5(D8)(C2)